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Key words: Psychotic disorders, Affective symptoms, Ultra High Risk, Cohort, Mediation

Abstract

We have previously reported an association between childhood sexual trauma and transition to psychosis in an Ultra High Risk (UHR) population. We aimed to investigate possible this association was mediated by affective or dissociative symptoms. Data were from a large UHR for psychosis cohort study. None of the potential mediators (depression, anxiety, dissociation, mood swings and mania, assessed by the HAM-D, HAM-A and the CAARMS symptom scales) significantly mediated the total association between sexual abuse scores and transition. At the point of transition, the mechanistic pathway from sexual trauma to psychosis does not appear to operate through affective symptoms.

1. Introduction

There is a well-established association between trauma and psychotic illness (Varese et al., 2012). Individuals with psychotic disorders who have experienced trauma show higher symptom levels and a poorer functional outcome than those who have not (Lysaker et al., 2005; Conus et al., 2010; Stain et al., 2014; Cotter et al., 2015). Trauma, including sexual trauma, appears to be a risk factor for later development of psychosis (Varese et al., 2012). Our own work in the Ultra High Risk (UHR) for psychosis group, in two separate samples, has shown that sexual trauma specifically (but not total trauma or other types of trauma) is associated with the later development of psychosis (Bechdolf et al., 2010; Thompson et al., 2014). This association holds after adjusting for possible confounding variables associated with

both trauma and the development of psychosis, including baseline levels of depression and anxiety (Thompson et al., 2014).

Understanding the mechanisms underlying the association between sexual trauma and subsequent development of psychosis in UHR samples is important for developing appropriate interventions. We have suggested a number of possible mechanisms to explain this association, including the possible roles of depression, anxiety and dissociation (Thompson et al., 2014). A prominent cognitive model of psychosis hypothesizes that the relationship between trauma and psychosis is influenced by dysphoric mood (Garety et al., 2001) and this may be true for all types of trauma. Other psychological models have highlighted that exposure to trauma during childhood may sensitize people in their reaction to later exposure to daily life stress (Lardinois et al, 2010), perhaps through altered stress sensitivity (Myin-Germeys et al, 2007). Others have highlighted the importance of dissociation in the relationship between trauma and development of psychotic symptoms (Varese et al, 2012). Mediation analysis, which assesses how a variable might be involved in the causal chain of an association as opposed to confounding the association, is a useful approach to investigating these hypotheses further.

This approach has been used to investigate the association between childhood trauma and psychosis (or psychotic symptoms) using data from birth cohorts or population samples. These reports suggest a number of possible mediators of the association, including social defeat (Van Nierop et al., 2014), attachment (Sitko et al., 2014), dysphoric mood (Marwaha and Bebbington, 2015), affective dysregulation

(Van Nierop et al., 2014; Marwaha and Bebbington, 2015), anxiety (Fisher et al., 2013) and negative self-schemas (Fisher et al., 2012). Affective symptoms appear to be the most commonly identified mediator.

These previous studies were conducted in birth cohorts (Fisher et al., 2012) and population-based samples (Van Nierop et al., 2014; Sitko et al., 2014; Marwaha and Bebbington, 2015;), and examined trauma more generally, rather than sexual trauma specifically (with the exception of Marwaha and Bebbington, 2015). None have investigated these mediation pathways in a sample of individuals at UHR for psychosis. It is reasonable to assume that the mediation pathways may be different in a clinical UHR sample compared to an unselected sample because the former are already presenting with attenuated psychotic symptoms. Therefore, we aimed to investigate whether previously identified factors also mediate the known association between sexual trauma and psychosis in our UHR sample. We hypothesized that affective symptoms would mediate the relationship in this sample.

2. Methods

2.1 *Sample*

These data are from the PACE 400 sample (N=416), a cohort of individuals aged 15-30 years who participated in research at the PACE clinic in Melbourne between 1993 and 2006, and who were followed up between 2.4 and 14.9 years later (mean time to follow-up 7.5 years). All participants in the cohort initially met the UHR criteria as assessed by the Comprehensive Assessment of At Risk Mental States

(CAARMS) (Yung et al., 2005). Follow-up interviews were performed with 311 (74.6%) of the sample and took place between July 2008 and July 2009. These interviews included the brief Childhood Trauma Questionnaire (CTQ) (N=233). The sample is described in detail in Nelson et al. (2013).

2.2 *Measures*

2.21 Independent variable

The brief CTQ (Bernstein et al., 2003) was completed at follow-up assessment (as outlined above). This is a 28-item self-report questionnaire that assesses the experience of specific early traumatic events "as a child and as a teenager". The CTQ has five subscales (physical abuse, sexual abuse, emotional abuse, physical neglect and emotional neglect) and provides a total score.

2.22 Dependent variable

Transition to psychotic disorder was determined using the CAARMS (Yung et al., 2005) using previously published cut-off points for psychosis threshold (Yung et al., 2003; Yung et al., 2004) for participants recruited after 1999. For early participants in research at PACE (N=59), transition was determined by cut-off scores on the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) and Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). The CAARMS threshold for psychosis was based on these thresholds and is therefore equivalent (Nelson et al., 2013). If CAARMS data were not available, the state public mental health records were accessed.

2.23 Proposed Mediator variables

The Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Depression Rating Scale (HAM-D) were completed at baseline in the cohort from 1993 to 2006. Post 2000, participants completed the CAARMS subscales for anxiety, depression, dissociation and mood swings, and lability and mania. These scales are rated 0-6 on intensity and 0-6 of frequency. We summed the intensity and frequency ratings to produce an overall rating of these items, as previously used (Yung et al., 2005).

2.3 *Statistical analysis*

Analyses were carried out using STATA 13. To test the role of different types of variables as mediators of the associations linking childhood sexual trauma to psychosis, we applied the Karlson Holm Breen (-khb-) command in Stata. This method of mediation analysis decomposes the total effect of a variable into direct and indirect effects (Breen et al., 2013) and can be used in logit and linear models. Mediators are hypothesized to occur as part of the pathway between an exposure and event as opposed to confounders, which moderate an association. Factors cannot usually be in both groups in a single analysis. The proposed mediation model tested is shown in Figure 1.

Insert Figure 1 around here

3. Results

The total number of participants with available data for each analysis is shown in Table 1. Detailed information on the sample with trauma and transition data is

detailed in Thompson et al (2014). The mean HAM-D and HAM-A baseline scores in this sample were 18.9 and 15.3.

The mediation models for the association between CTQ sexual abuse score and transition to psychosis as an outcome are shown in Table 1. The total effect refers to the model not accounting for mediators. The direct effect refers to the effect that is attributable to the direct association between sexual trauma and transition to psychosis. Indirect effect refers to the part of the total effect between sexual trauma and transition to psychosis explained by mediating variables (or the mediation effect). The p-values for the direct effects in the table demonstrated a significant direct association between sexual trauma and transition for 3 of the 7 of the mediator analysis samples (HAM-A, CAARMS rated mood swings, and mania). None of the proposed variables significantly mediated the total association between sexual abuse scores and development of psychosis. This is shown by the p>z values for all indirect effects for the 7 mediator variable analyses being greater than 0.05 in Table 1.

Insert Table 1 around here

4. Discussion

This investigation of the potential mediators of the association between sexual abuse and transition to psychosis in an UHR cohort found that there was no significant mediation by depressive and anxiety symptoms, dissociation, mood instability or mania. This finding is unexpected and does not align with the hypothesized role of anxiety symptoms and dysphoric mood in the pathway between trauma and

psychotic symptoms such as paranoia (Freeman and Fowler, 2009) and our own hypothesis. The findings are also contrary to those of Marwaha and Bebbington (2015) who reported an association between sexual abuse and psychotic disorder was significantly mediated by depression and anxiety.

This is the first investigation of affective and dissociative mediators of the association between sexual abuse and the transition to psychosis in an UHR sample. It may be that this finding is specific to clinical at-risk populations; these patients present with significant levels of other symptomatology and co-morbid diagnoses compared to other non-clinical high risk or birth cohort samples and are also different as they are help seeking. Depression and anxiety are common in UHR patients, with baseline rates of 41% and 15% respectively (Fusar-Poli et al., 2014). It is also known that comorbid depression and/ or anxiety in UHR samples do not appear to increase the risk of later transition to psychosis (Woods et al, 2009; Fusar-Poli et al, 2014) Thus, it may be that different mechanisms are responsible for conferring the risk of development of psychosis once the level of psychotic symptoms attracts clinical attention and the at-risk mental state is detected. Potential mechanisms include the role of externalizing bias (Bentall and Fernyhough, 2008); self-disturbance (Nelson et al., 2012; Haug et al., 2015); and biological vulnerabilities such as stress sensitivity and hippocampal abnormalities (Cotter et al., 2015). In other words, the mechanistic pathway, whether biological and/or psychological, from sexual trauma to psychosis transition in UHR patients, does not appear to operate via affective or dissociative disturbances. Given the wider literature, it is possible that sexual trauma leads to affective symptoms, but these in and of themselves are not critical in explaining the association between childhood

sexual trauma and transition to psychosis association at the "late initial stage" prodrome (Hafner et al., 2004).

4.1 *Strengths and limitations*

The strengths of this study are a large UHR sample with medium- to long-term follow-up. The limitations are that only a proportion of the sample completed the HAM-D and HAM-A scales or CAARMS scales at baseline and therefore the numbers for this analysis were reduced from the whole cohort. Additionally, the CAARMS indicators we used in the analysis are relatively crude and measure intensity and frequency of depression, anxiety, mood swings, mania and dissociation on a 0-6 scale. We therefore conclude that the negative finding for the role of dissociation, mania and mood swings using only data from this measure is less robust than the findings for depression and anxiety, where the finding is consistent across measures. Although the follow-up period was long (mean 7.5 years) and the majority of transitions will have likely occurred, the variability in length of follow-up should be acknowledged. Participants with available CTQ data were more likely to be female and slightly younger than those without CTQ data. Because females were more likely than males report sexual, emotional and total abuse, the current sample may be biased in this regard. There are other potential mediators that we have not included in the analysis such as cognition. Cognitive measures collected in the cohort were not consistent, making the use of these measures in mediation analyses difficult. There were minor modifications to the UHR criteria and instruments used to assess UHR criteria over the baseline recruitment period. Although we do not believe that this would have had a significant effect on whether

participants met UHR criteria, which UHR group they met, or transition risk, this has not been formally assessed.

4.2 *Clinical implications*

While sexual trauma is an important risk factor for transition to psychosis in the UHR population, this does not appear to be mediated by mood, anxiety, dissociative, or manic symptoms. Further investigation of possible mediators in this population (e.g., externalised attributional style, stress sensitivity, structural and functional neurobiological factors, etc.) is warranted to understand which interventions might help to mitigate this risk of progression to psychosis.

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Conflicts of Interest:

None

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Highlights

- Childhood sexual trauma was associated with later development of psychosis in an Ultra High Risk (UHR) for psychosis cohort
- This association was not mediated by depressive, anxiety or dissociative symptoms, nor by mood swings or manic symptoms
- At the point of transition, the mechanistic pathway from sexual trauma to psychosis does not appear to operate through affective symptoms.

Table 1: Effect of mediator variable on the total, direct and indirect effect between CTQ sexual abuse score and transition to psychosis

Effect	OR	Robust standard Error	z	p>z	95% CI
Mediator - HAM – A at baseline (n=79)					
Total effect	1.15	0.075	2.21	0.027	1.02 - 1.31
Direct effect	1.15	0.075	2.21	0.027	1.02 - 1.31
Indirect effect	1.00	0.007	-0.08	0.934	0.99 - 1.01
Mediator - HAM-D at baseline (n=141)					
Total effect	1.06	0.034	1.93	0.054	1.00 - 1.13
Direct effect	1.06	0.034	1.89	0.059	1.00 - 1.13
Indirect effect	1.00	0.003	0.40	0.687	1.00 - 1.01
Mediator - CAARMS mood item at baseline (n=138)					
Total effect	1.05	0.036	1.53	0.126	0.99 - 1.13
Direct effect	1.05	0.036	1.53	0.125	0.99 - 1.13
Indirect effect	1.00	0.003	-0.10	0.919	0.99 - 1.01
Mediator - CAARMS anxiety item at baseline (n=129)					
Total effect	1.06	0.037	1.73	0.083	0.99 - 1.14
Direct effect	1.07	0.038	1.83	0.068	1.00 - 1.14
Indirect effect	1.00	0.006	-0.66	0.509	0.98 - 1.01
Mediator - CAARMS dissociation item at baseline (n=70)					
Total effect	1.08	0.049	1.59	0.111	0.98 - 1.18
Direct effect	1.09	0.052	1.78	0.076	0.99 - 1.19
Indirect effect	0.99	0.012	-0.92	0.358	0.97 - 1.01
Mediator - CAARMS mood swings item at baseline (n=98)					
Total effect	1.09	0.041	2.17	0.030	1.01 - 1.17
Direct effect	1.09	0.041	2.22	0.027	1.01 - 1.17
Indirect effect	1.00	0.006	-0.34	0.730	0.99 - 1.01
Mediator - CAARMS mania item at baseline (n=64)					
Total effect	1.12	0.055	2.37	0.018	1.02 - 1.24
Direct effect	1.11	0.054	2.18	0.029	1.01 - 1.22
Indirect effect	1.01	0.014	0.78	0.438	0.98 - 1.04

Note: The total effect refers to the model not accounting for mediators. The direct effect refers to the effect that is attributable to the direct association between sexual trauma and transition to psychosis. Indirect effect refers to the part of the total effect between sexual trauma and transition to psychosis explained by mediating variables.

Figure 1: Proposed mediational model of sexual trauma and transition to psychosis in UHR subjects under test (HAM-D, Hamilton Depression Scale; HAM-A, Hamilton Anxiety Scale; CAARMS, Comprehensive Assessment of At Risk Mental States)